Formulation factors affecting acceptability of oral medicines in children

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Acceptability of medicines in children and caregivers affects safety and effectiveness of medicinal treatments. The pharmaceutical industry is required to demonstrate acceptability of new paediatric formulations in target age groups as an integrated part of the development of these products (P. Kozarewicz, 2014). Two questions arise when trying to tackle this task: "*which dosage form to choose for each target age group?*" and "*how to formulate it once the dosage form is decided?*". Inevitably, both the regulator and the developer turn to scientific evidence for answers. Research has emerged in recent years to demonstrate age-appropriateness and patient acceptability of different dosage forms; however, such information is still fragmented and far from satisfactory to define efficient formulation development strategies for a diverse patient subset (S. Ranmal and C. Tuleu, 2013). This paper highlights how formulation factors affect the acceptability of different oral medicines in children (Table 1), and it is based on a more extensive review article by Liu et al. (2014). Gaps in knowledge are highlighted in order to stimulate further research (F. Liu et al., 2014). In some areas, findings from studies conducted in adult populations may provide useful guidance for paediatric development and this is also discussed.

Tablets and capsules are the most commonly developed dosage forms for adult populations. Efforts have been made in recent years to understand the relationship between acceptable tablet sizes and the age group of children. However, insufficient data has been reported so far to draw a conclusion or recommendation on the right tablet size for the right age group which is also driven by indication, motivation of the patient and carer, counselling from health care professionals, as well as other factors. A more systematic approach would benefit future research to close the gaps in knowledge in this area. Investigation into the effects of other features of tablets, such as shape, colour and surface coating, on acceptability in children is scarce. Whilst future research is needed in this area, knowledge gained in adult populations provides useful references. The use of capsules in children and the associated formulation considerations has yet to gain extensive attention in research. The ability of

children to take capsules in comparison to tablets and how formulation features such as size and density of capsules affect a child's ability to swallow are the subjects of further research.

Oral liquids are traditionally appraised as the first formulation of choice for children who cannot swallow tablets and capsules. In recent years, shortcomings of liquids are recognised mainly including challenges in taste masking, stability issues and the use of numerous excipients, particularly preservatives. There is a consensus to move away from oral liquids to other flexible oral solid dosage forms such as multiparticulates and dispersible tablets (World Health Organisation, 2012). However, it should not be forgotten that oral liquids offer unique advantages including dose flexibility, ease of administration (usually no manipulation is required) and ease of ingestion. Moreover, their acceptance in children, and also with parents and healthcare professionals are well established as "the" paediatric medicine. The challenge is to apply innovative ideas to overcome the shortcomings of oral liquids and to optimise various characteristics of liquid formulations to improve acceptability, as listed in Table 1.

As mentioned above, oral flexible solid dosage forms have come into fashion in the field of paediatric formulations as they offer easier oral ingestion for youngsters compared to tablets and capsules, and avoid many drawbacks related to liquid formulations. It is important to understand the unique advantages of each of these dosage forms and the associated challenges in formulation development. Multiparticulate dosage forms are versatile in use. They are suitable for use to children from birth and provide flexible methods of administration, such as reconstitution into a drink or as "sprinkles" onto food. One risk associated with multiparticulates is chewing and this is particularly critical for modified release dosage forms. Particle size may be a "trigger" factor to initiate chewing response and the relationship between particle size and the risk of chewing needs investigation in future research. Dispersible, effervescent and chewable tablets share the same accountability of tooth erosion over the course of long-term use and the selection of

appropriate excipients is necessary to minimise such risks. Orally disintegrating tablets and films are relatively new innovations and have been proven to improve patient acceptance and compliance. The advance in these technologies could expand their application to a wider range of active ingredients and disease treatments.

Scientific evidence that could guide paediatric formulation development is lacking in the literature. Individual pharmaceutical companies gain experience and collect such data during product development and yet this is not available in the public domain. Regulatory bodies, academia and industry should work together to create an inventory of relevant parameters for oral formulation development to avoid duplication of efforts and provide consistent guidance.

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Table 1 Formulation factors affecting acceptability of oral dosage forms

Formulation platform	Summary of effects on acceptability
Tablet	
Size	Mini-tablets (2-4 mm) were reported to be acceptable for children from 6 months of age (V. Klingmann et al., 2013). Acceptability of tablets from 5 mm to 8 mm in size was evaluated in children from 1 to 11 years old in mixed age groups. Results from these studies were inconclusive as evidence for acceptability of tablets of different sizes in different age groups.
Shape	No report was found as to how tablet shape affects acceptability in children. Studies in adult populations show that patients' preference of tablet shape is associated with its size. Generally, small tablets are preferred to be arched round and medium and large tablets are preferred to be oblong or oval.
Film coating	Film coated and uncoated mini-tablets were both tested in children and two incidents of coughing or chocking were noted associating to coated tablets (V. Klingmann et al., 2013; S. A. Thomson et al., 2009). However, there is a lack of direct comparison of coated and uncoated tablets on swallowing performance in children.
Capsule	
Comparison with tablet	Direct comparison of acceptability of capsules with tablets in children has not been reported. Studies in adults show conflicting results; however, general caution when taking capsules was recommended due to the possibility of adhesion of the hydrated gelatin shell to oesophagus.
Size	Acceptability of capsules in children in relation to size has not been reported. Studies in adults show that oesophageal transit of capsules was not affected by capsule size, in contrast to the significant influence of tablet size on its transit.
Density	Effects of capsule density on swallowability in children were not reported. Studies in adults show that heavy capsules pass through the oesophagus significantly faster than light capsules.

Liquid	
Taste	Many reports and review articles have established that taste is fundamentally important in acceptability of liquid medicines in children.
Smell	The smell of a liquid has been associated to its flavour and could contribute to the palatability of liquid medicines. Limited data has been reported to link medication odour to acceptability in children.
Viscosity	No report was found on the effects of the viscosity of liquid medicines on acceptability and ease to swallow in children. Studies in adult populations and patients with dysphagia show that viscosity is associated to patient's perception of palatability of liquids. Thick liquids are deemed as unpleasant; however, these could improve swallowing safety in dysphagia patients.
Texture	The texture of a liquid, especially grittiness and mouth feel of suspensions has been linked to particle size. The effects on acceptability in children have not been extensively studied.
Volume	The ideal volume of liquid medicines should be swallowable in one unit. The average volume of liquid in one swallow is reported to be 4.5 ml in children from 15 months to 3.5 years of age (D. V. Jones and C. E. Work, 1961). Very small volumes of oral liquids could be related to issues in dosing accuracy in children.
Oral flexible solid dosage forms	
Multiparticulates	These are generally acceptable in children due to enhanced palatability and flexibility in administration such as mixing with semi-solid food. Grittiness and mouth feel are the main concerns in acceptability in children. The administration is considered to be time-consuming due to the need of reconstitution, which poses challenges to parents and carers.
Dispersible and effervescent tablets	Acceptability of dispersible tablets has been tested in children from 3 months to 8 years of age. These are generally more favourable compared to oral liquids such as syrup. However, the risk of tooth erosion needs to be considered for long-term use. The high quantity of sodium content in these formulations is associated to increased cardiovascular incidents in adults. The effect on long-term health in children has not been studied.

Orally disintegrating tablets	These are generally well accepted in children due to the improved possibility to formulate a dosage form with improved taste and texture, ease of use and reduced concern about difficulties in swallowing.
Chewable tablets	Chewable tablets are considered safe for children over the age of two years (T. M. Michele et al., 2002). The potential for tooth erosion over long-term use is still a consideration.